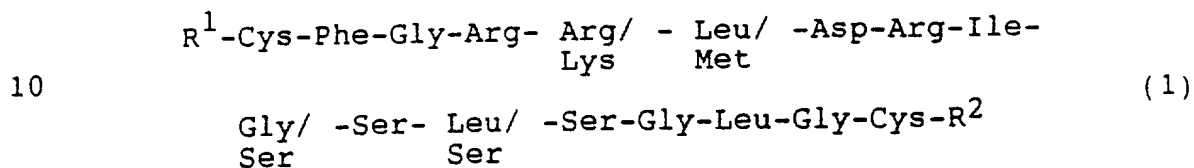


Claims

5

1. A peptide having natriuretic activity of the formula:



wherein R¹ is selected from the group consisting of:

15 (H);

Gly-;

Ser-Gly-;

20

Asp/
Lys/ -Ser-Gly-;
Gly

Arg/ Asp/
His/ - Lys/ -Ser-Gly-;
Gln Gly

25

Met/ Arg/ Asp/
Val - His/ - Lys/ -Ser-Gly-;
Gln Gly

30

Thr/ Arg/ Asp/
Met - Val - His/ - Lys/ -Ser-Gly-;
Gln Gly

Lys- Thr/ Arg/ Asp/
Met - Val - His/ - Lys/ -Ser-Gly-;
Gln Gly

35

Pro-Lys- Thr/ Arg/ Asp/
Met - Val - His/ - Lys/ -Ser-Gly-;
Gln Gly

Ser-Pro-Lys- Thr/ - Met/ - Arg/ Asp/
Met Val Gln Gly -Ser-Gly-;

5 or a 10- to 109-amino acid sequence shown as the native upstream sequence for porcine, canine or human BNP in Figure 8, or a composite thereof;

R^2 is (OH), NH_2 , or $NR'R''$ wherein R' and R'' are independently lower alkyl (1-4C) or is

10

Asn/
Lys

Asn/ -Val
Lys

15

Asn/ -Val-Leu
Lys

Asn/ -Val-Leu-Arg
Lys

20

Asn/ -Val-Leu-Arg- Arg/
Lys Lys

Asn/ -Val-Leu-Arg- Arg/ - Tyr/
Lys Lys His

or the amides (NH_2 or $NR'R''$) thereof,
with the proviso that if formula (1) is

25

R^1 -Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-
Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys- R^2

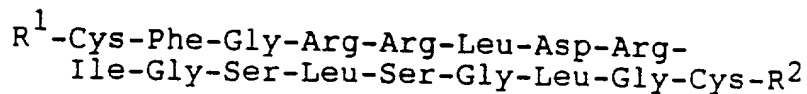
and R^1 is Asp-Ser-Gly-, R^2 cannot be Asn-Val-Leu-Arg-Arg-Tyr.

30

2. A peptide having natriuretic activity which is a modified form of the peptide of claim 1, having conservative amino acid substitutions in one or two positions.

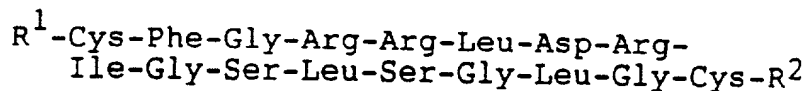
35

3. The peptide of claim 1 having the formula:

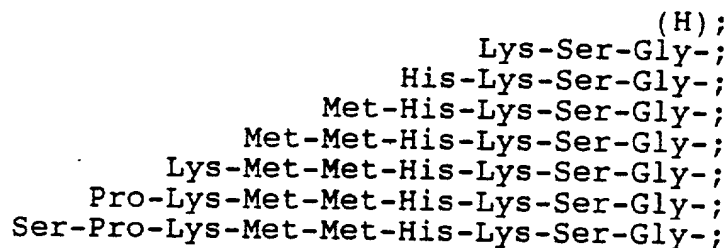


wherein R^1 is selected from Thr-Met-Arg-Asp-Ser-Gly; Ser-Pro-Lys-Thr-Met-Arg-Asp-Ser-Gly; and Gly-Ile-Arg-Ser-Pro-Lys-Thr-Met-Arg-Asp-Ser-Gly; and the 10- to 108-amino acid upstream sequence shown for porcine prepro-BNP in Figure 8.

4. The peptide of claim 1 having the formula

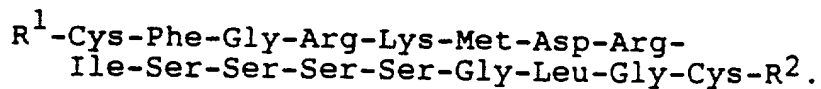


wherein R^1 is selected from

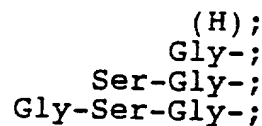


and the 10- to 109-amino acid sequence shown for canine BNP in Figure 8.

5. The peptide of claim 1 having the formula



6. The peptide of claim 5 wherein R^1 is selected from



5 Gln-Gly-Ser-Gly-;
 Val-Gln-Gly-Ser-Gly-;
 Met-Val-Gln-Gly-Ser-Gly-;
 Lys-Met-Val-Gln-Gly-Ser-Gly-;
 Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-;
 Ser-Pro-Lys-Met-Met-His-Lys-Ser-Gly-;

and the 10- to 109-amino acid sequence shown for human BNP
in Figure 8.

10 7. A recombinant DNA in isolated form consisting
essentially of a DNA which encodes the peptide of claim 1.

8. A recombinant expression system capable, when
contained in a recombinant host cell, of expressing the DNA
15 encoding the peptide of claim 1.

9. A recombinant host cell or cell culture which
has been manipulated so as to contain the expression system
of claim 8.

20 10. A method to produce a peptide having
natriuretic activity, which method comprises:
 culturing the cells of claim 9 under conditions
which permit the expression of the DNA encoding said
25 peptide; and
 recovering the peptide from the culture.

11. A pharmaceutical composition useful in
treating conditions associated with a high level of
30 extracellular fluid which composition comprises an effec-
tive amount of the peptide of claim 1 in admixture with a
suitable pharmaceutical excipient.

12. A method to treat a condition characterized
35 by a high level of extracellular fluid which comprises
administering to a subject in need of treatment an effec-

tive amount of the peptide of claim 1 or a pharmaceutical composition thereof peptide.

5 13. The method of claim 12 wherein the condition is congestive heart failure.

10 14. A pharmaceutical composition useful in treating conditions associated with a high level of extracellular fluid which composition comprises an effective amount of the peptide of claim 6 in admixture with a suitable pharmaceutical excipient.

15 15. A method to treat a condition characterized by a high level of extracellular fluid which comprises administering to a subject in need of treatment an effective amount of the peptide of claim 6 or a pharmaceutical composition thereof.

20 16. The method of claim 15 wherein the condition is congestive heart failure.

25 17. A DNA probe useful in retrieving the gene encoding brain natriuretic peptide from a vertebrate DNA library, which probe comprises the pBNP-encoding cDNA shown in Figure 1, or an effective portion thereof.

30 18. A DNA sequence encoding a peptide having natriuretic activity, which DNA hybridizes directly or indirectly with the probe of claim 17 at 42°C in buffer containing 20% formamide, 5 x Denhardt's, 6 x SSC, 100 mg/ml RNA, 0.05% Na pyrophosphate, followed by washing at 60°C at 1 x SSC, 0.1% SDS.

35 19. A peptide having natriuretic activity encoded by a DNA, which DNA hybridizes directly or in-

5 directly with the probe of claim 17 at 42°C in buffer
containing 20% formamide, 5 x Denhardt's, 6 x SSC, 100 mg/
ml RNA, 0.05% Na pyrophosphate, followed by washing at 60°C
at 1 x SSC, 0.1% SDS,

with the proviso that said peptide is not pBNP.

10 20. A DNA sequence which comprises a segment of
contiguous or non-contiguous portions of the cDNA of Figure
1, which segment encodes a brain natriuretic peptide having
natriuretic activity.

15 21. The DNA of claim 20 wherein the segment
encodes pBNP.

22. The DNA of claim 20 wherein the segment
encodes the peptide sequence Thr-Met-Arg-pBNP.

20 23. The DNA of claim 20 wherein the segment
encodes the peptide sequence Ser-Pro-Lys-Thr-Met-Arg-pBNP.

25 24. The DNA of claim 20 wherein the segment
encodes the peptide sequence Gly-Ile-Arg-Ser-Pro-Lys-Thr-
Met-Arg-pBNP.

30 25. A DNA sequence which comprises a modified
segment of contiguous or non-contiguous portions of the
cDNA of Figure 1 wherein said modified segment encodes a
BNP having one or two conservative amino acid substitu-
tions.

35 26. A recombinant expression system which
comprises the segment of claim 20 operably linked to
control sequences functional in a recombinant host.

27. A recombinant host transformed with the expression system of claim 26.

5 28. A method to produce a recombinant brain natriuretic peptide which comprises culturing the transformed host of claim 27 under conditions suitable for the expression of the BNP and,
10 recovering BNP from the culture.

29. Recombinant BNP produced by the method of claim 28, with the proviso that said BNP is not pBNP.

15 30. A brain natriuretic peptide which is a modification of a BNP encoded by a segment of contiguous or non-contiguous portions of the cDNA of Figure 1 wherein one or two positions contain conservative amino acid substitutions.

20 31. The BNP of claim 30 wherein one of said substitutions is substitution of the D- for the L-form.

25

30

35